Part Three. Intracellular Signaling

19. G Proteins

Eric J. Nestler and Ronald S. Duman

Heterotrimeric G Proteins
- Multiple forms of heterotrimeric G proteins exist in the nervous system
- Each G protein is a heterotrimer composed of single α, β and γ subunits
- The functional activity of G proteins involves their dissociation and reassociation in response to extracellular signals
- G proteins couple some neurotransmitter receptors directly to ion channels
- G proteins regulate intracellular concentrations of second messengers
- G proteins have been implicated in membrane trafficking
- G protein β,γ subunits subserve numerous functions in the cell
- The functioning of heterotrimeric G proteins is modulated by several other proteins such as RGS proteins
- G proteins are modified covalently by the addition of long-chain fatty acids

Small G Proteins
- The best characterized small G protein is the Ras family, a series of related proteins of ~21 kDa
- Rab is a family of small G proteins involved in membrane vesicle trafficking

Other Features of G Proteins
- G proteins may be involved in disease pathophysiology
- G proteins may be regulated by psychotropic drugs

References

20. PHOSPHOINOSITIDES

Anne M. Heacock and Stephen K. Fisher

INTRODUCTION

THE INOSITOL LIPIDS

- The three quantitatively major phosphoinositides are structurally and metabolically related
- The quantitatively minor 3-phosphoinositides are synthesized by phosphatidylinositol 3-kinase.
- Phosphatidylinositol 4,5-bisphosphate is cleaved by a family of phosphoinositide-specific phospholipase C isozymes
- Cleavage of phosphatidylinositol 4,5-bisphosphate initiates two interlinked cycles: one in which the DAG backbone is conserved and recycled, and another in which inositol is reutilized

THE INOSITOL PHOSPHATES

- D-myo-Inositol 1,4,5-trisphosphate is a second messenger that liberates Ca^{2+} from the endoplasmic reticulum via intracellular receptors
- The metabolism of inositol phosphates leads to regeneration of free inositol
- Highly phosphorylated forms of myo-inositol are present in cells

DIACYLGLYCEROL

- Protein kinase C, a widely distributed enzyme, is activated by diacylglycerol
- Diacylglycerol is a breakdown product of both phosphoinositides and other lipids

PHOSPHOINOSITIDES AND CELL REGULATION

- Inositol lipids can serve as mediators of other cell functions, independent of their role in signal transduction

BOX: Does the inhibitory action of Li^+ on inositol monophosphate breakdown explain the therapeutic action of Li^+ in manic-depressive psychosis?

REFERENCES

21. Cyclic Nucleotides

Ronald S. Duman and Eric J. Nestler

The Second-Messenger Hypothesis

Adenylyl Cyclases

Multiple forms of adenylyl cyclase exist in the nervous system
The different forms of adenylyl cyclase are similar in structure
Adenylyl cyclases are regulated by Gas and Gai
Adenylyl cyclase subtypes also are regulated by b,g subunits
Adenylyl cyclases show differential regulation by Ca2+
Adenylyl cyclases are regulated upon phosphorylation
Adenylyl cyclase is subject to long-term regulation in the nervous system

Guanylyl Cyclase

Membrane-bound forms of guanylyl cyclase are plasma membrane receptors
Soluble forms of guanylyl cyclase are activated by nitric oxide
Nitric oxide functions as a second messenger

Cyclic Nucleotide Phosphodiesterases

There are multiple forms of phosphodiesterase in brain
Phosphodiesterases show a distinctive molecular structure
Phosphorylation is a primary mechanism for regulation of phosphodiesterase activity
Phosphodiesterase inhibitors show promise as pharmacotherapeutic agents

Functional Roles for cAMP and cGMP

Most of the effects of cAMP on cell function are mediated via protein phosphorylation
Some ion channels are regulated directly by cAMP
The mechanisms by which cGMP produces its physiological effects are more varied

Future Perspectives

References

22. Serine and Threonine Phosphorylation

James A. Bibb and Eric J. Nestler

Protein Phosphorylation is of Fundamental Importance in Biological Regulation
- Regulation of protein phosphorylation involves a protein kinase, a protein phosphatase and a substrate protein

Protein Serine-Threonine Kinases
- Protein kinases differ in their cellular and subcellular distribution, substrate specificity and regulation
- A major class of serine-threonine kinases are regulated by second messengers
- The mitogen-activated protein kinase cascade is second messenger-independent
- Most protein serine-threonine kinases undergo autophosphorylation

Protein Serine-Threonine Phosphatases
- The brain contains multiple forms of protein serine-threonine phosphatases
- Protein serine-threonine phosphatases play a critical role in the control of cell function
- Protein phosphatase 1 and protein phosphatase 2A are regulated by protein phosphatase inhibitor proteins
- Mitogen-activated protein kinase phosphatases are dual-function protein phosphatases

Neuronal Phosphoproteins
- Virtually all types of neuronal proteins are regulated by phosphorylation
- Protein phosphorylation is an important mechanism of memory
- Neuronal phosphoproteins differ considerably in the number and types of amino acid residues phosphorylated
- The phosphorylation of a protein can influence its functional activity in several ways

Cellular Signals Converge at the Level of Protein Phosphorylation Pathways

Protein Phosphorylation Mechanisms in Disease
- Abnormal phosphorylation of specific neural proteins may contribute to the development of Alzheimer's disease
- Upregulation of the cAMP pathway is one mechanism underlying opiate addiction

References

23. Calcium

Gary Bird and James Putney Jr.

The Concept of Ca^{2+} as a Cellular Signal

Measurement of Cellular Ca2+ Concentrations and Movements

Ca^{2+} Regulation at the Plasma Membrane

Two distinct mechanisms for controlling [Ca^{2+}] at the plasma membrane are a Ca^{2+}-ATPase pump and a Na^{+}- Ca^{2+} exchanger.

Ca^{2+} Stores and Ca^{2+} Pools

The only known mechanism for accumulation of Ca^{2+} by the endoplasmic reticulum is through the actions of SERCA pumps.

Mitochondria may accumulate Ca^{2+} by an energy-dependent process

Calcium is stored at other significant sites in the cell.

Ca^{2+} Signaling

Release of intracellular Ca^{2+} is mediated primarily via inositol 1,4,5-trisphosphate receptors and ryanodine receptors.

Ca2+ enters cells either via voltage-dependent or voltage-independent channels.

Periodic temporal and spatial patterns of Ca^{2+} signaling give rise to calcium oscillations and waves.

Although distinct, Ca^{2+}-signaling events in excitable and nonexcitable cells share some common characteristics.

Ca^{2+}-Regulated Processes

Ca^{2+} is required for acute cellular responses, such as contraction or secretion.

Ca^{2+} also plays a role in more prolonged cellular events, such as mitogenesis and apoptosis.

References

24. Tyrosine phosphorylation

Lit-fui Lau and Richard L. Huganir

1. Tyrosine phosphorylation in the nervous system—General Introduction

2. Protein tyrosine kinases
    a. Nonreceptor protein tyrosine kinases
        i. Unique domain
        ii. SH3
        iii. SH2
        iv. SH1
        v. Regulation of kinase activities
    b. Receptor protein tyrosine kinases
        i. Extracellular domain
        ii. Transmembrane domain
        iii. Cytoplasmic domain
        iv. Regulation of kinase activities

3. Protein tyrosine phosphatases
    a. Nonreceptor protein tyrosine phosphatases
    b. Receptor protein tyrosine phosphatases

4. Tyrosine phosphorylated substrates
    a. Ligand-gated ion channels
        i. Acetylcholine receptor
        ii. NMDA receptor
        iii. GABA receptor
    b. Voltage-gated ion channels
        i. potassium channels
        ii. sodium channels
        iii. voltage-gated cationic channel

5. Role of tyrosine phosphorylation in the nervous system
    a. Survival and differentiation
    b. Axonal guidance
    c. Synapse formation and plasticity
        i. Neuromuscular junction
            1. agrin
            2. ARIA
        ii. Central synapses
            1. ephrinB-ephB
            2. BDNF
    d. Neurological disorders